

### **AMENDMENTS TO THE CLAIMS**

*The listing of claims will replace all prior versions and listings of claims in the application:*

#### **Listing of Claims:**

1-200. (Canceled)

201. (New) A synthetic siRNA for interacting with a target mRNA of a target gene, the siRNA comprising:

    a sense strand comprising:

        a sense region;

        a first nucleotide of the sense strand closest to the 5' end of the sense strand having a 2'-O-alkyl modification; and

        a second nucleotide of the sense strand next closest to the 5' end of the sense strand having a 2'-O-alkyl modification; and

    an antisense strand comprising an antisense region which is at least substantially complementary with the mRNA of the target gene and the sense region; and

202. (New) The siRNA of claim 201, wherein a first nucleotide of the antisense strand closest to the 5' end of the antisense strand is phosphorylated at its 5' end and the sense strand is devoid of a phosphate at its 5' end.

203. (New) The siRNA of claim 202, further comprising a second nucleotide of the antisense strand next closest to the 5' end of the antisense strand having a 2' modification and the first nucleotide of the antisense strand having a 2' modification.

204. (New) The siRNA of claim 203, wherein the 2' modification on the first nucleotide and the second nucleotide of the antisense strand is a 2'-O- alkyl modification.

205. (New) The siRNA of claim 204, wherein the 2'-O-alkyl modification is a 2'-O-methyl modification for each of the first and second nucleotides of the sense and antisense strands, and all nucleotides in the sense and antisense regions other than the first and second nucleotides of the sense and antisense strands have a 2'-OH.

206. (New) The siRNA of claim 202, wherein the antisense region includes at least one nucleotide having a 2' modification, wherein the 2' modification in the antisense region is selected from the group consisting of 2'-O-alkyl, 2'-deoxy, 2'-amine, 2'-alkyl, and 2'-fluoro.

207. (New) The siRNA of claim 206, wherein the 2'-O-alkyl modification on the first and second nucleotides of the sense strand is a 2'-O-methyl modification and the 2' modification on the at least one nucleotide in the antisense region is a 2'-O-methyl modification.

208. (New) The siRNA of claim 202, wherein all nucleotides in the sense and antisense regions other than the first and second nucleotides of the sense strand each have a 2'-OH.

209. (New) The siRNA of claim 202, wherein a third nucleotide in the sense strand has a 2'-O-alkyl modification, the third nucleotide being immediately next to the second nucleotide from the 5' end of the sense strand.

210. (New) The siRNA of claim 204, wherein the sense and antisense strands each has a third nucleotide that is immediately next to the second nucleotide from the 5' end of each strand, each third nucleotide has a 2'-O-alkyl modification.

211. (New) The siRNA of claim 210, wherein the 2'-O-alkyl modification is a 2'-O-methyl modification for the first, second, and third nucleotides of the sense and antisense strands and all nucleotides in the sense and antisense regions other than the first, second, and the third nucleotides of the sense and antisense strands have a 2'-OH.

212. (New) The siRNA of claim 202, wherein at least one nucleotide of the sense region other than the first or second nucleotide from the 5' end of the sense strand is a pyrimidine nucleotide

having a 2'-O-alkyl modification, and at least one nucleotide of the antisense region is a pyrimidine nucleotide having a 2' halogen modification.

213. (New) The siRNA of claim 202, wherein the antisense strand has at least one phosphorothioate internucleotide linkage.

214. (New) The siRNA of claim 202, wherein the antisense strand has at least one methylphosphonate internucleotide linkage.

215. (New) The siRNA of claim 212, wherein the 2' halogen modification is a 2'-O-fluorine modification, and the 2'-O-alkyl modification in the first, second, and the modified pyrimidine nucleotides of the sense strand is a 2'-O-methyl modification.

216. (New) The siRNA of claim 204, wherein at least one nucleotide of the sense region other than the first or second nucleotide from the 5' end of the sense strand is a pyrimidine nucleotide having a 2'-O-alkyl modification, and at least one nucleotide of the antisense region other than the first and second nucleotides from the 5' end of the antisense strand is a pyrimidine nucleotide having a 2' halogen modification.

217. (New) The siRNA of claim 216, wherein the antisense strand has at least one phosphorothioate internucleotide linkage.

218. (New) The siRNA of claim 216, wherein the antisense strand has at least one methylphosphonate internucleotide linkage.

219. (New) The siRNA of claim 216, wherein the 2' halogen modification of the pyrimidine nucleotide is a 2' fluorine modification, and the 2'-O-alkyl modification in the first and second nucleotides of the sense and antisense strands and the 2'-O-alkyl modification of the modified pyrimidine nucleotide in the sense strand is a 2'-O-methyl modification.

220. (New) The siRNA of claim 202, further comprising a 3' overhang of 1-5 nucleotides on at least one of the sense or antisense strand.

221. (New) The siRNA of claim 220, wherein the 3' overhang has at least one phosphorothioate internucleotide linkage or at least one methylphosphonate internucleotide linkage.

222. (New) The siRNA of claim 204, further comprising a 3' overhang of 1-5 nucleotides on at least one of the sense or antisense strand.

223. (New) The siRNA of claim 222, wherein the 3' overhang has at least one phosphorothioate internucleotide linkage or at least one methylphosphonate internucleotide linkage.

224. (New) The siRNA of claim 202, further comprising at least one conjugate molecule coupled to the sense or antisense strand.

225. (New) The siRNA of claim 224, wherein the conjugate is cholesterol.

226. (New) The siRNA of claim 203, further comprising at least one conjugate molecule coupled to the sense or antisense strand.

227. (New) The siRNA of claim 226, wherein the conjugate is cholesterol.

228. (New) A synthetic siRNA for interacting with a target mRNA of a target gene, the siRNA comprising:

- a sense strand comprising:

- a sense region;

- a first nucleotide of the sense strand closest to the 5' end of the sense strand having a 2'-O-alkyl modification and being devoid of a phosphate at its 5' end; and

- a second nucleotide of the sense strand next closest to the 5' end of the sense strand having a 2'-O-alkyl modification; and

- an antisense strand comprising:

an antisense region which is at least substantially complementary with the mRNA of the target gene and the sense region;

a first nucleotide of the antisense strand closest to the 5' end of the antisense strand having a 2'-O-alkyl modification and a phosphate at its 5' end; and

a second nucleotide of the antisense strand next closest to the 5' end of the antisense strand having a 2'-O-alkyl modification.

229. (New) A synthetic siRNA for interacting with a target mRNA of a target gene, the siRNA comprising:

a sense strand comprising:

a sense region;

a first nucleotide of the sense strand closest to the 5' end of the sense strand having a 2'-O-alkyl modification and being devoid of a phosphate at its 5' end;

a second nucleotide of the sense strand next closest to the 5' end of the sense strand having a 2'-O-alkyl modification; and

at least one pyrimidine nucleotide of the sense strand having a 2'-O-alkyl modification, wherein the pyrimidine nucleotide is a nucleotide other than said first or second nucleotides of the sense strand; and

an antisense strand comprising:

an antisense region which is at least substantially complementary with the mRNA of the target gene and the sense region;

a first nucleotide of the antisense strand closest to the 5' end of the antisense strand having a 2'-O-alkyl modification and a phosphate at its 5' end;

a second nucleotide of the antisense strand next closest to the 5' end of the antisense strand having a 2'-O-alkyl modification; and

at least one pyrimidine nucleotide other than the first and second nucleotides of the antisense strand having a 2'-halogen modification.

230. (New) The siRNA of claim 229, further comprising a 3' overhang of 1-5 nucleotides on at least one of the sense or antisense strand.

231. (New) The siRNA of claim 230, wherein the antisense strand has at least one phosphorothioate internucleotide linkage or at least one methylphosphonate internucleotide linkage.

232. (New) The siRNA of claim 229, further comprising at least one conjugate molecule coupled to the sense or antisense strand.

233. (New) The siRNA of claim 232, wherein the conjugate is cholesterol.